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### **REMARKS**

Claims 21 and 35 are presently pending and under examination.

Claim 21 is directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF- $\beta$ -induced production and deleterious accumulation of extracellular matrix in a tissue by contacting the tissue with an anti-TGF- $\beta$  antibody that binds to TGF- $\beta$ ; whereby the binding of the anti-TGF- $\beta$  antibody to the TGF- $\beta$  suppresses the deleterious accumulation of the TGF- $\beta$ -induced extracellular matrix in the tissue, and wherein the pathology or condition is glomerulonephritis. Claim 35 is directed to a method for treating a pathology characterized by an accumulation of extracellular matrix in a tissue, comprising contacting said tissue with a TGF- $\beta$  suppressing agent which suppresses the extracellular matrix producing activity of TGF- $\beta$ , wherein said pathology is adult respiratory distress syndrome and wherein said agent is an TGF- $\beta$  antibody.

### **Regarding 35 U.S.C. § 103(a)**

#### **Regarding Claim 21**

The rejection of claim 21 under 35 U.S.C. §103(a) as allegedly rendered obvious by U.S. Patent No. 5,772,998 to Dasch et al., in view of U.S. Patent No. 5,583,103, to Ruoslahti et al. and/or Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) is respectfully traversed.

Claim 21 is directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF- $\beta$ -induced production and deleterious accumulation of extracellular matrix in a tissue by contacting the tissue with an anti-TGF- $\beta$  antibody that binds to TGF- $\beta$ ; whereby the binding of the anti-TGF- $\beta$  antibody to the TGF- $\beta$  suppresses the deleterious accumulation of the TGF- $\beta$ -

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induced extracellular matrix in the tissue, and wherein the pathology or condition is glomerulonephritis.

To establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Erlich*, 3 U.S.P.Q.2d 1011, 1016 (Bd. Pat. App. & Int. 1986). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

For the reasons set forth below, the assertion that it would have been obvious for one skilled in the art to combine the cited references to arrive at Applicants' claimed invention is not accompanied by the required showing of where the cited references disclose the desirability of making the specific combination that is Applicants' presently claimed invention. Establishing that the prior art would have suggested the claimed method requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (quoting *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); see also *C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the

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specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (quoting *In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant's own disclosure. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d 994, 999 ("[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight"). In determining the validity of patented biopsy needle assembly over the sole assertion that it arose from obvious adaptations of a single prior art needle assembly to accommodate a new biopsy gun design, the court admonished against hindsight reconstruction when it stated:

The invention that was made, however, does not make itself obvious; that suggestion or teaching must come from the prior art. See, e.g., *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52, 5 USPQ2d 1434, 1438 (Fed.Cir.1988) (it is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed.Cir.1985) (it is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor); *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed.Cir.1985) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

The court went on to conclude that because no prior art provided a teaching, suggestion or motivation for the structure of the claimed needle assembly there was, as a matter

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of law, an absence of an essential evidentiary component for an obviousness finding. *C.R. Bard* at 1352.

Applicants respectfully maintain that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness.

First, the prior art references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content.

Second, the prior art references upon which the Office relies to support the present rejection, when viewed in combination, do not provide the skilled person with a reasonable expectation of success to achieve the claimed invention.

The Dasch et al. '998 patent describes a method of neutralizing the inhibitory effects of TGF- $\beta$  and further references several species of pathologies, including interstitial lung fibrosis, liver cirrhosis, fibrotic skin disorders such as scleroderma and scarring. Far from containing a suggestion of the claimed method of decreasing the deleterious TGF- $\beta$  induced accumulation of extracellular matrix (ECM) associated with glomerulonephritis by contacting a tissue with an anti TGF  $\beta$  antibody that binds to TGF- $\beta$ , Dasch et al. does not even contain a reference to glomerulonephritis.

The secondary reference U.S. Patent No. 5,583,103, to Ruoslahti et al., is a continuation of application Ser. No. 07/467,888, filed on Jan. 22, 1990, subsequently abandoned, which is a continuation-in-part of application Ser. No. 07/212,702, filed Jun. 28, 1988. The priority document application Serial No. 07/212,702, attached hereto as Attachment A for the Examiner's convenience, which is the only document in the lineage that predates the priority date of the above-identified application, describes use of the proteoglycan decorin to treat cell proliferation and sets forth glomerulonephritis as a disease with a proliferative component. The only reference to TGF- $\beta$  in the '702 disclosure is a statement in the introductory paragraph of the background section that TGF- $\beta$  is a multifunctional factor that **inhibits growth of some cell types**, but can also stimulate cell proliferation. Significantly, Ruoslahti et al. does not teach or

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suggest the inhibition of TGF- $\beta$  activity for the purpose of decreasing the deleterious accumulation of the ECM or any of its components nor does it suggest that glomerulonephritis is associated with TGF- $\beta$  induced accumulation of extracellular matrix (ECM).

The secondary reference by Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988), does not teach or suggest the use of any agent, including anti-TGF- $\beta$  antibody, *in vivo* or in a tissue nor does the reference mention glomerulonephritis. Bassols et al. does not teach or suggest the inhibition of TGF- $\beta$  activity for the purpose of decreasing the deleterious accumulation of the ECM or any of its components nor does it suggest that glomerulonephritis is associated with TGF- $\beta$  induced accumulation of extracellular matrix (ECM).

Taken together, the prior art references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content. In particular, nowhere in the references is provided a motivation for combining the references because there is no suggestion that glomerulonephritis is associated with TGF- $\beta$  induced extracellular matrix accumulation. Without the benefit of Applicants' disclosure, the combination of references provides no suggestion that it is possible to decrease the deleterious accumulation of extracellular matrix associated with glomerulonephritis by contacting the tissue with an anti TGF  $\beta$  antibody that binds to TGF- $\beta$  and suppresses the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix in a tissue. Absent such a suggestion, there is no motivation for combination of the references without the use of impermissible hindsight construction based on Applicants' disclosure. Furthermore, the skilled person familiar with the cited references would not have had a reasonable expectation of success with regard to suppressing the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix in a tissue by administering an anti-TGF- $\beta$  antibody to treat glomerulonephritis. Accordingly, a *prima facie* case of obviousness has not been established and the rejection of claim 21 as rendered obvious by the cited references is unsupported and should properly be withdrawn.

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Regarding Claim 35

The rejection of claim 35 under 35 U.S.C. §103(a) as allegedly rendered obvious by U.S. Patent No. 5,772,998 to Dasch et al., in view of Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) and Raghu et al., *Am. Rev. Respir. Dis.* 131:281-289 (1985) is respectfully traversed.

Claim 35 is directed to a method for treating a pathology characterized by an accumulation of extracellular matrix in a tissue, comprising contacting said tissue with a TGF- $\beta$  suppressing agent which suppresses the extracellular matrix producing activity of TGF- $\beta$ , wherein said pathology is adult respiratory distress syndrome and wherein said agent is an TGF- $\beta$  antibody.

The references by Dasch et al. and Bassols et al. are described above. Briefly, with regard to adult respiratory distress syndrome, far from containing a suggestion of the claimed method of decreasing the deleterious TGF- $\beta$  induced accumulation of extracellular matrix (ECM) associated with adult respiratory distress syndrome by contacting a tissue with an anti TGF  $\beta$  antibody that binds to TGF- $\beta$ , the Dasch et al. '998 patent makes no reference to adult respiratory distress syndrome.

Implicit in the section 103 rejection is that Dasch contains deficiencies that are cured by Bassols et al. and Raghu et al. However, the deficiencies in Dash et al. are not cured by either Bassols et al. or Raghu et al. Bassols et al., does not teach or suggest the use of any agent, including anti-TGF- $\beta$  antibody, *in vivo* or in a tissue nor does the reference mention adult respiratory distress syndrome. Raghu et al. describes the distribution and composition of extracellular matrix components, including collagen types I and III in normal and fibrotic human lungs. The reference does not teach or suggest any involvement of TGF- $\beta$  in adult respiratory distress syndrome and in fact, at page 285, center column, concedes a lack of understanding of the underlying mechanisms and pathogenesis:

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The entire process of lung injury-interstitial fibrosis in ARDS occurred during the period of a few days to a few weeks, whereas the process in IPF was a more gradual phenomenon occurring in the course of several months to years. The rapidity of onset of pulmonary-fibrosis in ARDS is well noted. **The triggering mechanisms and the pathogenesis of pulmonary fibrosis remain unknown in both conditions.**

(Citation omitted; emphasis added)

The prior art references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content. In particular, nowhere in the references is provided a motivation for combining the references because there is no suggestion that adult respiratory distress syndrome is associated with TGF- $\beta$  induced extracellular matrix accumulation. Without the benefit of Applicants' disclosure, the combination of references provides no suggestion of the possibility of suppressing the accumulation of extracellular matrix associated with adult respiratory distress syndrome by contacting the tissue with an anti TGF  $\beta$  antibody that binds to TGF  $\beta$  and suppresses the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix in a tissue. Absent such a suggestion, there is no motivation for combination of the references without the use of impermissible hindsight construction based on Applicants' disclosure. Furthermore, the skilled person familiar with the cited references would not have had a reasonable expectation of success with regard to suppressing the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix in a tissue by administering an anti-TGF- $\beta$  antibody to treat ARDS. Accordingly, a *prima facie* case of obviousness has not been established and the rejection of claim 35 as rendered obvious by the cited references is unsupported and should properly be withdrawn.

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Regarding claims 21 and 35

For the reasons already stated above, Applicants traverse the rejection of claim 21 under 35 U.S.C. §103(a) as allegedly rendered obvious by U.S. Patent No. 5,772,998 to Dasch et al., in view of U.S. Patent No. 5,583,103, to Ruoslahti et al. and/or Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) as well as the separate rejection of claim 35 as allegedly rendered obvious by U.S. Patent No. 5,772,998 to Dasch et al., in view of Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) and Raghu et al., *Am. Rev. Respir. Dis.* 131:281-289 (1985).

Applicants submit that the instant rejection which appears to apply U.S. Patent No. 5,772,998 to Dasch et al., in view of U.S. Patent No. 5,583,103, to Ruoslahti et al. and/or Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) to claim 21, and apply U.S. Patent No. 5,772,998 to Dasch et al., in view of Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988) and Raghu et al., *Am. Rev. Respir. Dis.* 131:281-289 (1985) to claim 35, appears redundant to the individual rejections addressed above, with the exception of Applicants' alleged statement at pages 18-24 of the Brief on Appeal submitted March 3, 2002 (Paper No. 80), and at page 13 of the Reply Brief submitted August 13, 2002 (Paper No. 82), that the species glomerulonephritis and ARDS are rendered obvious by the generic method of using an anti TGF- $\beta$  antibody that binds to TGF- $\beta$  to suppress the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix.

Applicants respectfully submit that the Examiner takes out of context the arguments set forth in Applicants' briefs on appeal, which were directed at showing prior invention of the generic method claimed at the time of the appeal and further submits that Applicant's Appeal Brief is not citable in lieu of a reference to support a prior art rejection. Therefore, the prior art rejections are identical to those separately addressed above.



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### **Regarding Priority of Invention**

Applicants maintain that the previously submitted Rule 131 Declaration and supporting evidence are sufficient to show prior invention of the glomerulonephritis and ARDS species presently claimed. Without conceding priority of invention for the glomerulonephritis and ARDS species, Applicants nevertheless submit that the pending claims are unobvious over the cited references, obviating the issue of priority of invention.

In section 9, at page 18, of the current Office Action, the Office cites the Board's statement that the issue of priority of invention cannot be resolved through use of a Rule 131 Declaration, but can only be resolved through an interference. Applicants submit that based on the claim amendments made in Applicants' Rule 196 submission following the appeal decision, the subject matter presently pending is not the same as that claimed in the '998 patent, as evidenced by the Office's withdrawal of the rejections under section 102 of the Code, such that an Interference proceeding is no longer an issue.

### **Regarding Provisional Double-Patenting**

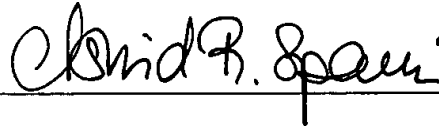
Applicants acknowledge and defer responding to the provisional rejection of claims 21 and 35 under the judicially created doctrine of obviousness-type double patenting over co-pending application Serial No. 08/345,865.

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**CONCLUSION**

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to contact the undersigned attorney.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Astrid R. Spain", is written over a horizontal line.

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Attachment A – U.S. Application Ser. No. 07/212,702; filed Jun. 28, 1988